Treatment of severe asthma in adolescents and adults

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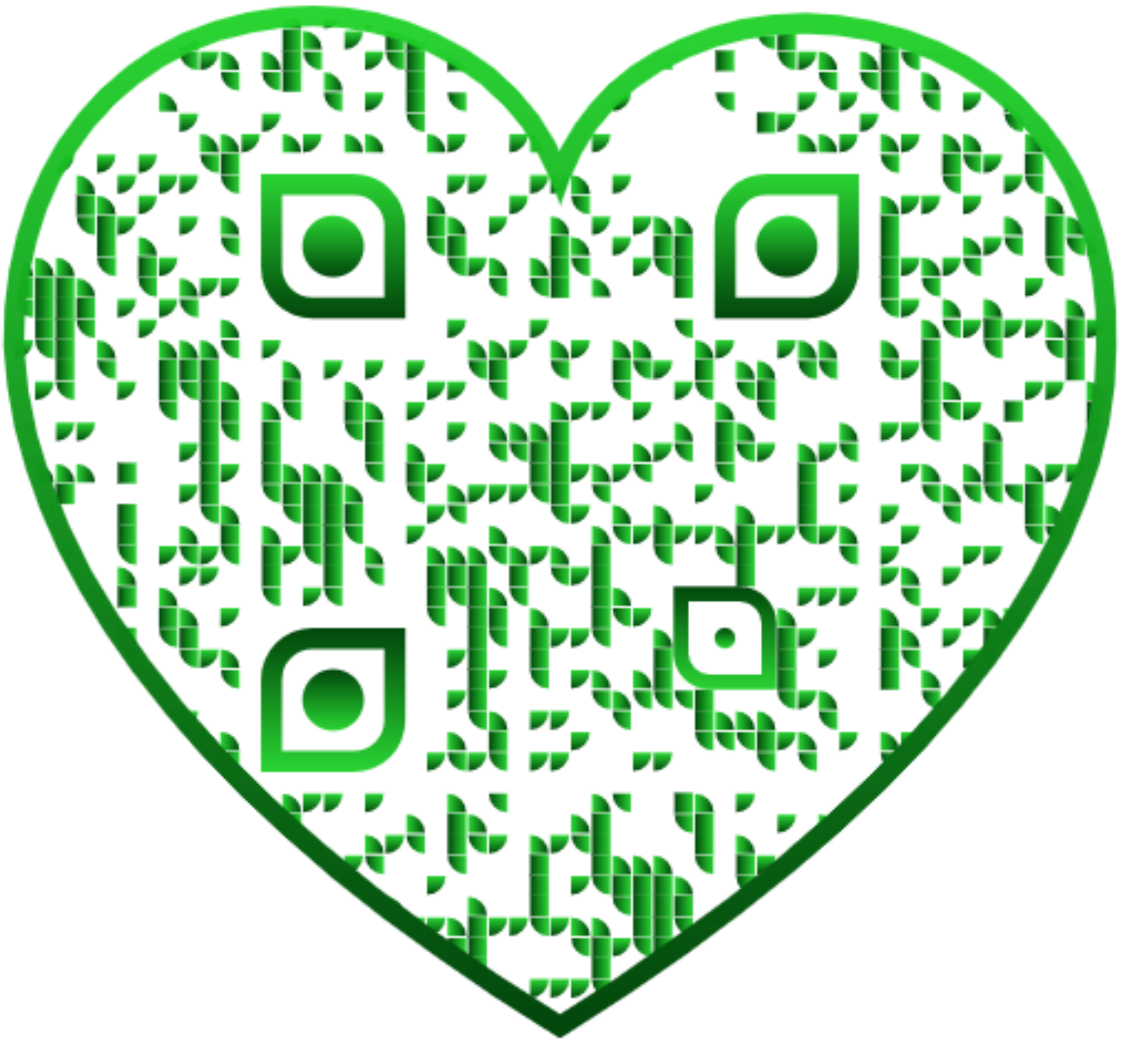
What's New

Gaps in guideline-based asthma care in patients with uncontrolled severe asthma (August 2024)

The burden of asthma falls disproportionately on the 20 to 50 percent of patients with severe asthma who remain poorly controlled despite therapy. These patients require specialist care, and many may benefit from initiation of biologic therapies. In a new United States database study that identified over 90,000 patients with poorly controlled severe asthma, between 35 and 51 percent did not receive a specialist visit or medication escalation in response to an asthma hospitalization or two separate exacerbations requiring systemic glucocorticoids [1]. An even smaller proportion of the non-White population received such interventions. These observations suggest a significant gap in delivery of guideline-recommended care to this high-risk group of patients. (See "Treatment of severe asthma in adolescents and adults", section on 'Triage'.)

INTRODUCTION

The classification of "severe asthma," according to European Respiratory Society (ERS)/American Thoracic Society (ATS) criteria, refers to patients who require high-dose inhaled glucocorticoid (GC) plus a second controller or continuous or near



continuous oral GC treatment to maintain asthma control and those who never achieve control despite that treatment (table 1) [1,2].

The evaluation of patients with severe asthma symptoms, a general overview of asthma management, and a review of nonpharmacologic management are presented separately. (See "Evaluation of severe asthma in adolescents and adults" and "An overview of asthma management in children and adults" and "Trigger control to enhance asthma management".)

Treatment issues that pertain to patients with severe asthma are reviewed here, while treatment approaches to mild and moderate persistent asthma are reviewed separately. (See "An overview of asthma management in children and adults" and "Initiating asthma therapy and monitoring in adolescents and adults" and "Ongoing monitoring and titration of asthma therapies in adolescents and adults".)

GENERAL TREATMENT PRINCIPLES

Treatment of severe asthma frequently requires a multidisciplinary approach to address patient education needs, remediate irritant and allergic triggers, treat comorbidities, and design an optimal medication regimen.

Triage — For patients with difficult to control severe asthma, referral to specialist centers for further assessment leads to improved asthma control, reduced exacerbations, and decreased oral corticosteroid use [3-6]. Nevertheless, a substantial proportion of patients with uncontrolled severe asthma do not receive specialist visits or medication escalation after significant exacerbations [7]. The benefits of specialist evaluation are likely only increasing in recent years with the expansion of biologic treatment options.

Patient education — A written asthma action plan is recommended for all patients with severe asthma (form 1) [8]. Either a symptom or peak flow-based plan may be used; although evidence shows similar benefits, patients who are poor perceivers of dyspnea may benefit from a plan based on objective measure of airflow limitation. We frequently provide a prescription for a short course of prednisone (eg, 40 mg daily for

five days) for patients to keep on hand and to start based on specific criteria in their action plan. (See "Asthma education and self-management".)

Patients may still not know how to use their inhalers correctly despite a long history of asthma; each patient's technique should be observed, and correct technique carefully demonstrated for each type of inhaler used. (See "The use of inhaler devices in adults" and "Delivery of inhaled medication in adults".)

Compliance/adherence — Compliance/adherence to medications should be addressed at each visit, in partnership with the patient [9]. There are many reasons for nonadherence. Strategies to maintain adherence can be discussed while developing the action plan. If a medication is not subjectively or objectively improving the patient's symptoms or respiratory function after a three-month trial, it should be stopped. (See "Enhancing patient adherence to asthma therapy".)

Controlling asthma triggers — Ongoing exposure to asthma triggers is an important cause of poor asthma control in some patients. For patients with severe asthma who have no allergic component to their disease, allergen control measures will have little to no effect. Potential triggers that are identified during evaluation (eg, pets, dust mites, workplace exposures, tobacco smoke) need renewed strategies for control (table 2). (See "Trigger control to enhance asthma management" and 'Treatment of comorbidities' below.)

Treatment of comorbidities — If comorbid conditions that may influence a patient's response to asthma treatment are identified, every effort should be made to control their impact. However, evidence that this will improve the course of a patient's asthma is limited.

- Allergic rhinitis should be treated with allergen avoidance and intranasal glucocorticoids (GCs) [10,11]. If surgically amenable naso-sinus disease (eg, chronic rhinosinusitis in a patient with nasal polyposis) is identified, then referral to an otolaryngologist should be considered. (See "Chronic rhinosinusitis without nasal polyposis: Management and prognosis".)
- Symptomatic gastroesophageal reflux disease (GERD) should be treated with proton pump inhibitors, although data to suggest that this therapy improves asthma (as opposed to GERD) are limited. Therapy with proton pump inhibitors

does not improve asthma-related outcomes in patients who do not have symptoms of GERD. (See "Initial management of gastroesophageal reflux disease in adults" and "Gastroesophageal reflux and asthma", section on 'Management of patients without symptoms of GERD'.)

- Inducible laryngeal obstruction (also known as vocal cord dysfunction or paradoxical vocal fold motion), when present with severe asthma, should be treated by a knowledgeable speech therapist. Underlying causes (eg, postnasal drip, GERD, and anxiety) should be treated. (See "Inducible laryngeal obstruction (paradoxical vocal fold motion)".)
- Patients who smoke should be counseled that this is a risk factor for fatal asthma and that cessation is imperative. Smoking cessation classes, counseling, and pharmacologic aids may be helpful [12]. (See "Overview of smoking cessation management in adults" and "Identifying patients at risk for fatal asthma".)
- Treatment of obstructive sleep apnea may improve nocturnal symptoms of dyspnea and choking [13-15]. (See "Clinical presentation and diagnosis of obstructive sleep apnea in adults".)
- Obese patients may benefit from counseling regarding ways to improve nutrition and increase activity [16-18]. In an unblinded trial, 33 obese patients with severe asthma were randomly assigned to treatment for obesity or usual care [18]. After six months, the treatment group had lost 7.88 kg and had significant improvements in asthma control based on the Asthma Control Questionnaire (ACQ). In certain cases, obesity may be so severe that bariatric surgery is considered [17,19,20], but in patients on chronic oral GCs, there are likely to be increased complications with this approach as well. (See "Obesity and asthma".)
- Allergic bronchopulmonary aspergillosis can complicate severe asthma and should be evaluated in patients with a blood eosinophil count >500 cells/microL and/or total serum IgE >417 international units/mL. (See "Clinical manifestations and diagnosis of allergic bronchopulmonary aspergillosis".)
- Anxiety and depression (or other psychiatric issues) should be evaluated and treated [21].

Monitoring — Once a regimen has been developed, we usually request that patients with severe asthma return for follow up visits at four- to eight-week intervals. We evaluate control using standardized questions, either the Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT) (form 2) [22-24]. Objective measures of airflow limitation (eg, peak expiratory flow, spirometry) are important; spirometry may need to be performed more frequently than in patients with milder asthma. In particular, we perform spirometry when there is a significant change in clinical status and to confirm that a step-down in medication has not caused a clinically silent decline in lung function. Spirometry may also have utility in comparing the efficacy of various add-on controller agents.

SHORT-ACTING BETA-AGONISTS

Inhaled short-acting beta-agonists (SABAs) should be prescribed for the relief of acute symptoms [2,8,25]. Albuterol, at a dose of 2 to 4 puffs, is commonly prescribed, although other equivalent agents are available (table 3). This dose may be repeated twice within an hour if needed for an acute exacerbation. SABAs should only be used on an as needed basis. (See "Beta agonists in asthma: Acute administration and prophylactic use".)

Some patients with severe asthma derive better symptom relief from nebulized albuterol, compared with the metered dose preparation. Patients should be advised to seek emergency department evaluation, if they are unimproved after two home nebulizer treatments within an hour.

INITIAL CONTROLLER THERAPY

Some patients presenting with symptoms and objective measures consistent with National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA) definitions of severe asthma are not on controller therapy (table 4) (see 'Introduction' above) [8,25]. With addition of controller medication, many will improve enough that they do not meet criteria for severe asthma (table 1). This section will describe our approach to such patients.

Initial controller agents for severe asthma include oral and inhaled glucocorticoids (GCs) and long-acting beta-agonists. Generally, combination therapy with two or more controller agents will be needed to achieve improved control in patients with severe asthma.

Achieving the usual goals of asthma treatment (prevent chronic and troublesome symptoms, normalize pulmonary function, maintain normal activity levels, prevent exacerbations, improve health-related quality of life, and provide optimal pharmacotherapy with minimal or no adverse effects) may not be fully possible in patients with severe asthma. It may be necessary to accept some degree of reduced activity and persistent airflow limitation, and to focus instead on reducing the frequency and severity of exacerbations and hospitalizations, avoiding further loss of pulmonary function, and limiting toxicity from medications.

Oral glucocorticoids — Most patients who are not on any controller medication and meet GINA criteria for step 4 therapy or NAEPP criteria for "severe persistent asthma" will need an initial, brief course of oral GC therapy to bring their asthma under control (table 4) [8,25]. In deciding when to prescribe oral GC, we consider the severity of symptoms, degree of airflow limitation, and whether symptoms have been stable or worsening. In general, we prescribe a brief course of an oral GC to patients with frequent daytime or nocturnal symptoms, recent deterioration (eg, increased need for short-acting beta-agonists [SABAs]), or a forced expiratory volume in one second (FEV_1) less than 60 percent of predicted. The treatment of acute asthma exacerbations is discussed separately. (See "Acute exacerbations of asthma in adults: Home and office management".)

A re-evaluation in two weeks will assess the response to therapy and determine the need for longer term, low-dose oral GC versus transition to inhaled GC alone.

A two-week course of oral GC or an intramuscular injection of triamcinolone [26] may also be considered in patients who have baseline stable airflow obstruction that does not reverse with inhaled bronchodilator. In this way, the degree of reversibility to GCs can be determined. The FEV_1 at the end of the trial may be used as a goal for ongoing controller therapy, instead of the usual target of 80 percent of the predicted value.

Inhaled glucocorticoids — Inhaled GCs (called inhaled corticosteroids [ICS] in the NHLBI guidelines) that are high potency and used at a high dose are the foundation of long term controller therapy in severe asthma (table 5 and table 6) [8,22,27,28]. Several formulations are available; we usually choose one from the "high potency" group that allows for the least number of puffs per day. (See "Delivery of inhaled medication in adults".)

The dose of inhaled GC is adjusted at subsequent visits based on asthma control. (See 'Adjusting controller therapy' below.)

Combination inhaled GC/LABA — Most patients with severe asthma are treated with a combination of inhaled GC and a LABA (salmeterol, formoterol, or vilanterol) (table 6) [8,25,27]. (See 'Combination inhaled GC/LABA' below.)

ADJUSTING CONTROLLER THERAPY

Once a patient who presents with severe asthma is receiving controller therapy with inhaled glucocorticoids (GCs) and a long-acting beta-agonist (LABA), subsequent visits are usually scheduled at four- to eight-week intervals. At these visits, therapy is adjusted based upon an assessment of asthma control and any adverse effects of medication, remembering that the degree of asthma control is determined by the most severe indicator of impairment (table 7 and table 8) [29].

Explanations for persistent symptoms despite high-dose combination therapy include residual inflammation that is relatively GC resistant, remodeling (not inflammation) that is causing airflow limitation, and inflammation in the distal airways that is not reached by the inhaled GCs. At this point, we consider several choices, which are discussed in more detail in the sections that follow:

- Trying a course of oral GC or an intramuscular injection of triamcinolone. (See 'Systemic glucocorticoids' below.)
- Increasing the inhaled GC dose up to 1600 to 2000 mcg per day. (See 'Inhaled glucocorticoids' above.)
- Substituting an alternate or adding a third controller agent, such as an antileukotriene agent or tiotropium. (See 'Antileukotriene agents' below and

'Inhaled GC/LAMA or GC/LAMA/LABA' below.)

- Referral to an asthma specialist for assessment of asthma phenotype and consideration of therapy with one of the biologic agents. (See 'Persistently uncontrolled asthma' below.)
- If asthma remains poorly controlled, experimental therapies may be considered in the context of clinical trials. (See 'Selecting among biologic agents' below and 'Experimental approaches' below and "Investigational agents for asthma".)

Systemic glucocorticoids — Oral GCs are the most potent and effective controller agent for asthma, but have substantial side effects when used for months to years [8,25,30]. Even recurrent intermittent use of systemic glucocorticoids is associated with development of osteoporosis, pneumonia, cardiovascular disease, cataracts, and type 2 diabetes in a dose-dependent manner [31]. We always try to use the lowest dose of oral GC for the shortest duration possible, because of the side effects of systemic GCs. We use high-dose inhaled GC, LABA, and other controller medications to maintain asthma control and allow tapering of oral GC, because these other controller medications have fewer systemic effects.

When a patient has frequent exacerbations despite high doses of inhaled GCs, it is occasionally helpful to determine whether the patient's asthma is actually responsive to GCs. This can be accomplished with injection of a long-acting GC, such as triamcinolone [32]. With this approach, adherence/compliance is no longer an issue. In a randomized trial, patients with a high level of lung eosinophils, despite high-dose inhaled (and even oral) GCs, responded to 3 mL (40 mg/mL) of intramuscular triamcinolone acetonide with improved forced expiratory volume in one second (FEV_1), reduced rescue medication, and decreased lung eosinophils when assessed two weeks later [26]. Patients who respond to triamcinolone are not steroid resistant, but often poorly adherent or poorly steroid responsive, requiring very high doses of GC that may be associated with substantial side effects. After intramuscular triamcinolone, the anti-inflammatory effect and hypothalamic-pituitary-adrenal suppression last for about two to six weeks. It is reasonable to reassess symptom control and spirometry in three to four weeks.

Patients who fail to respond to systemic GCs may rarely have GC resistant asthma. For clinical purposes, this is defined by a FEV_1 that is less than 75 percent of predicted and fails to improve by 15 percent after a two-week trial of oral GC (eg, prednisone 40 mg per day). (See "Mechanisms and clinical implications of glucocorticoid resistance in asthma".)

Consideration should be given to daily low-dose oral GCs (5 to 10 mg/day) when bursts of oral GCs are required every two to three months despite high-dose inhaled GC, long-acting inhaled beta-agonist, and trials of other controller agents described below. However, even low doses of oral corticosteroids are associated with increased risk of comorbidities, hospitalizations, and mortality in patients with asthma [33], so they should only be used at the minimum necessary dose when other approaches have failed to control asthma symptoms or exacerbations. Patients on chronic oral GC need to be monitored for GC side effects. (See "Major adverse effects of systemic glucocorticoids".)

This use of systemic GCs has been supplanted in many eligible patients by the biologics which have reported systemic GC sparing effects (anti-IL-5,5R and anti-IL-4R). However, economic/insurance issues may still limit their use, and not all eligible patients respond sufficiently. (See 'Persistently uncontrolled asthma' below.)

Inhaled glucocorticoids — Inhaled GCs have broad anti-inflammatory effects in asthma and are effective in many patients with severe asthma [8,25,34,35]. They have been shown to reduce asthma symptoms; improve peak expiratory flow (PEF), spirometry, and quality of life; diminish airway hyperresponsiveness; and prevent or reduce the frequency of exacerbations. We usually use a high potency GC that allows for the least number of puffs per day. (See "Delivery of inhaled medication in adults".)

When asthma is not well controlled on high-dose inhaled GC (eg, about 1000 mcg per day), but appears to be GC responsive, we consider a further increase in dose or use of an inhaled GC with a smaller particle size. The evidence for increasing the dose of inhaled GC above 1000 mcg per day is limited and not all patients will improve with higher inhaled GC doses. As an example, a double blind, parallel group study of 671 patients with severe asthma found slightly greater efficacy with fluticasone 2 mg per day compared to fluticasone 1 mg per day or to budesonide 1.6 mg per day [36].

Outcome measures were morning peak flow, rescue medication, daily symptom scores and diurnal peak flow variation. However, systemic GC side effects are likely to occur in this dose range.

Monitoring for GC related side effects is appropriate for patients on chronic high-dose inhaled GC. (See "Major side effects of inhaled glucocorticoids".)

Combination inhaled GC/LABA — Most patients with severe asthma should receive a trial of combination therapy with inhaled GC and a long-acting beta-agonist (LABA) [8,25,27]. These can be prescribed as a combination inhaler (preferred) or as separate inhalers (table 6 and table 8).

The evidence in favor of combined GC/LABA therapy comes largely from extrapolation from trials in patients with moderately severe asthma and a few trials that studied addition of a LABA in patients with severe asthma [27,37-39]. In contrast, one randomized trial found only minimal improvement with addition of salmeterol or formoterol to high-dose inhaled or oral GC treatment [40].

Clinical trials and systematic reviews are increasingly reassuring about the safety of LABAs when used with inhaled GC in fixed-combination inhalers, and in late 2017 the United States Food and Drug Administration (FDA) removed the “boxed warning” that expressed concerns about the safety of these medications [41]. LABAs are never used as monotherapy in severe asthma. (See "Beta agonists in asthma: Acute administration and prophylactic use", section on 'Evidence of LABA-ICS safety'.)

If asthma symptoms, SABA use, and objective measures are unimproved after a trial of LABA therapy, consideration should be given to stopping the LABA.

Antileukotriene agents — Evidence for the efficacy of leukotriene modifying agents (LTMAs) as add-on therapy in severe asthma is limited [42-45]. One study evaluated the leukotriene receptor antagonist (LTRA) montelukast as additive therapy in patients whose asthma was not controlled with inhaled GC and LABA and did not find a benefit, but the study duration was only two weeks [43]. On the other hand, we believe that LTMAs are often helpful in patients with late onset disease, particularly those with aspirin-exacerbated respiratory disease (AERD) [46,47]. If a LTRA does not improve asthma control within three months, we frequently try the 5-lipoxygenase

inhibitor zileuton as an alternative [48,49]. (See "Aspirin-exacerbated respiratory disease", section on 'Leukotriene-modifying agents'.)

The National Asthma Education and Prevention Program (NAEPP) guidelines also suggest a trial of an antileukotriene agent in patients with severe asthma who are not controlled on high-dose inhaled GC and LABA [8].

Currently available agents include the 5-lipoxygenase inhibitor zileuton (Zyflo) and the CysLT receptor antagonists (LTRAs) montelukast (Singulair) and zafirlukast (Accolate) (table 9). (See "Antileukotriene agents in the management of asthma".)

Inhaled GC/LAMA or GC/LAMA/LABA — For adults with one or more asthma exacerbations in the past year despite use of a GC-LABA inhaler, addition or substitution of a LAMA is suggested [2]. The LAMA can be provided as a separate tiotropium inhaler or as a triple GC-LAMA-LABA inhaler.

Tiotropium — Tiotropium, a once daily inhaled long-acting muscarinic-antagonist (LAMA) that is widely used for COPD, is approved by the FDA for long-term maintenance treatment in asthma, at a dose of 2.5 mcg/day (two inhalations of 1.25 mcg by soft mist inhaler) [50]. Tiotropium is suggested as add-on therapy for patients whose asthma is not controlled with inhaled GC-LABA (step 4 to 5), although the benefit may be small and variable [25,51]. We typically reserve tiotropium for patients who have ongoing asthma symptoms (and ongoing short-acting beta-agonist [SABA] use) and exacerbations despite combination therapy with inhaled GC-LABA. For these patients, we typically stop the LABA and institute a trial with a LAMA, as the benefits of adding a LAMA to inhaled GC-LABA are limited, and the effect on symptoms is inconsistent. This is particularly relevant in patients who are taking additional SABAs three to four times per day, despite LABA therapy.

Evidence in favor of using a LAMA for severe asthma is modest and based primarily on improvement in lung function as observed in a number of randomized trials and systematic reviews [52-58].

- One systematic review (4 trials, 1197 participants) found that adding tiotropium to LABA-inhaled GC reduced exacerbations compared with adding placebo, although the confidence interval included the possibility of no difference (OR

0.76, 95% CI 0.57-1.02) [57]. Quality of life was not significantly improved, but lung function was improved.

- A subsequent systematic review (15 trials, 7122 participants) found that adding a LAMA (virtually always tiotropium) to inhaled glucocorticoids reduced exacerbations compared with adding placebo (RR 0.67, 95% CI 0.48-0.92; absolute risk reduction 2 percent), but adding a LAMA to inhaled glucocorticoids did not reduce exacerbation risk compared with adding a LABA (RR 0.87, 95% CI 0.53-1.42) [58]. Furthermore, adding a LAMA to a LABA-inhaled GC regimen did not reduce exacerbation risk significantly compared with adding placebo (RR 0.84, 95% CI 0.57-1.22), but the FEV_1 trough was increased with triple therapy (mean difference 0.07L [95% CI 0.01-0.14]).

Concern about possible harm from tiotropium comes from the BELT trial in which inhaled GC plus tiotropium was compared with inhaled GC plus twice-daily LABA [55]. While no difference was observed in the time to first exacerbation, or control of asthma symptoms, the rate of asthma-related hospitalizations was higher in the tiotropium group.

The main adverse effect of tiotropium in these asthma trials was dry mouth. In the first of the trials above, drug-related cardiac events occurred in two patients in the tiotropium group and one in the placebo group.

Combination inhaled GC/LAMA/LABA — The once daily triple agent dry powder inhaler, fluticasone furoate-umeclidinium-vilanterol (FF/UM/VI; note fluticasone furoate has greater anti-inflammatory potency per mcg than fluticasone propionate), comes in two dose strengths (FF 100 mcg/UM 62.5 mcg/VI 25 mcg **or** FF 200 mcg/UM 62.5 mcg/VI 25 mcg) and is approved by the FDA for use in moderate-to-severe asthma (table 6)[59].

- **Fluticasone-umeclidinium-vilanterol** – Triple therapy with FF/UM/VI was examined in a randomized trial (CAPTAIN) that assigned 2439 adults with poorly controlled asthma despite using a GC/LABA combination to one of six groups: FF/UM/VI (100/31.25/25 mcg; 100/62.5/25 mcg; 200/31.25/25 mcg; 200/62/25 mcg) or fluticasone furoate-vilanterol (FF/VI; 100/25 mcg; 200/25 mcg) [60]. Addition of UM 62.5 mcg to FF/VI (100/25 mcg or 200/25 mcg) led to an increase

in FEV_1 (least mean squares 110 mL [95% CI 66-153]; 92 mL [95% CI 49-135], respectively); but the decrease in exacerbations did not reach significance. Results were similar with the lower dose of UM. Among patients with higher blood eosinophil levels, preparations with FF 200 mcg led to a 65 percent (95% CI 29.6 to 82.8) lower rate of moderate-to-severe exacerbations, compared with preparations with FF 100 mcg, suggesting the glucocorticoid dose is the most important of the three elements for reducing exacerbations.

Two other triple combination inhalers are under investigation:

- **Beclomethasone-glycopyrronium-formoterol** – Beclomethasone-glycopyrronium-formoterol (BDP/GL/FO), was examined in two parallel, 52-week randomized trials (TRIMARAN and TRIGGER) [61]. In TRIMARAN, 1155 patients were assigned to BDP/GL/FO (100/10/6 mcg) or BDP/FO (100/6 mcg), two inhalations twice daily. In TRIGGER, 1437 patients were assigned to BDP/GL/FO (200/10/6 mcg) or BDP/FO (200/6 mcg), two inhalations twice daily, or open-label BDP/FO (200/6 mcg, two inhalations twice daily) plus tiotropium 2.5 mcg two inhalations once daily. In TRIMARAN, the rate of moderate to severe exacerbations was decreased by 15 percent in the triple therapy group (rate ratio 0.85, 95% CI 0.73-0.99). In TRIGGER, exacerbations were lower with triple therapy but did not reach significance (RR 0.88, 95% CI 0.75-1.03). Lung function was modestly improved with triple therapy, but the change in FEV_1 did not reach clinically significant thresholds.

  Of note, the nomenclature for glycopyrrolate/glycopyrronium varies among countries, as does the expression of dosing (table 10).

- Mometasone-glycopyrrolate-indacaterol – In a 52-week trial with 3092 patients, the combination inhaler mometasone-glycopyrrolate-indacaterol (MF/GL/IND; 160/50/150 mcg) once daily resulted in a 65 mL greater increase in FEV_1 compared with high-dose mometasone-indacaterol (MF/IND; 160/150 mcg) once daily and a 119 mL greater increase in FEV_1 compared with fluticasone-salmeterol(FP/S 500/50 mcg) taken twice daily [62].

PERSISTENTLY UNCONTROLLED ASTHMA

Some patients have persistently uncontrolled asthma despite high-dose inhaled glucocorticoids and one or more nonglucocorticoid controller medications. Biologic therapies targeting the underlying airway inflammation have revolutionized treatment for this group of patients. In longitudinal cohorts, approximately 80 percent of patients experience a ≥50 percent reduction in exacerbations and/or maintenance oral glucocorticoids following initiation of biologic therapy [63,64]. In one cohort, nearly one-quarter of patients were able to achieve normal lung function, no exacerbations over 12 months, and cessation of maintenance oral glucocorticoids [63]. Nevertheless, nearly 50 percent of patients continue to experience partially uncontrolled disease after biologic initiation [64], so these medications should not be introduced as a panacea for severe disease.

Selecting among available biologic agents (anti-immunoglobulin E [anti-IgE] therapy, anti-interleukin-5 [anti-IL-5], anti-IL-5R, anti-IL-4R, or anti-thymic stromal lymphopoietin [TSLP] treatments) depends on several clinical factors including age, serum IgE level, and Type-2 asthma phenotype, as described in the following sections (table 11) [2,51,65,66].

Bronchial thermoplasty is generally reserved for patients who are not candidates for or have not responded to an optimal controller regimen or biologic agents for asthma, meet other specific criteria described below, and are willing to accept the risks of the procedure [51]. (See 'Bronchial thermoplasty' below.)

Selecting among biologic agents — The biologic agents for severe asthma have not been compared in head-to-head trials, and indirect comparisons have shown variable results [63,67-71]. Each agent has its own particular indications, dosing, and side effect profile based on clinical trials (table 11). As examples, only patients with an IgE level ≥30 international units/mL and testing evidence of atopy are candidates for omalizumab; only patients with an elevated eosinophil count (>150 cells/ml) are candidates for anti-IL4R, anti-IL-5 or anti-IL5R therapies; and only adults are eligible for some agents.

Beyond meeting required indications, characterizing the underlying type of inflammation or asthma phenotype can help guide selection of therapy (algorithm 1). As an example, patients in the pivotal trials of omalizumab,

dupilumab, and tezepelumab who also had an elevated fractional exhaled nitric oxide (FeNO) ≥25 ppb showed more robust responses to these agents compared with other patients in these trials [72-74]. For patients with severe asthma but without elevated FeNO or allergen-driven symptoms, tezepelumab still demonstrates efficacy [74]. Further description and characterization of severe asthma phenotypes are presented separately. (See "Characterizing severe asthma phenotypes".)

To help guide biologic selection, we typically perform the following work-up:

- Assess history of childhood versus adult-onset asthma (we use onset at age >12 years to define adult onset)
- Assess sensitivity to inhaled perennial allergens by history and either skin-prick or allergen specific blood IgE testing
- Obtain peripheral blood eosinophil count, total IgE levels, and FeNO

Repeated measurements of FeNO, blood eosinophil count (BEC), or IgE may be useful in those with low levels on a single test, as patients with intermittently elevated levels of type 2 biomarkers are common and appear to have similar exacerbation patterns as those with persistent elevations [75-78]. We also test for geographic- and travel-appropriate chronic helminthic infection, as this can complicate biologic therapy.

For patients who are already maintained on chronic oral glucocorticoids, certain biologics have been shown to be more effective at reducing glucocorticoid dependence over time than others (algorithm 2) [79]. Verifying the diagnosis of asthma and characterizing asthma phenotype in these patients often requires discontinuing or decreasing oral glucocorticoids to unmask underlying disease features. This can be avoided if historical data prior to oral glucocorticoid use are available. For patients without these records or who have been on systemic glucocorticoids for more than 24 months, we typically stop or taper low-dose (5 to 10 mg) oral glucocorticoids with a plan to re-evaluate type 2 markers and pulmonary function testing as soon as symptoms significantly worsen. Typical testing includes assessment of peripheral eosinophils, FeNO, spirometry with bronchodilator reversibility, lung volumes (to assess hyperinflation and air-trapping), and (if spirometry is normal) methacholine challenge. Patients without evidence of bronchodilator reversibility or response to methacholine challenge should not receive

biologic agents and should be re-evaluated for pulmonary diagnoses other than asthma.

Some patients will meet criteria for more than one medication, and there is only indirect evidence to guide which agent will generate the best response. Indirect analysis from clinical trial data suggests a relatively similar effect of dupilumab and the anti-IL-5/5R agents [67]. In general, indirect comparison studies using large databases have somewhat favored dupilumab over omalizumab and anti-IL5/5R agents in terms of exacerbation reduction [69-71]; however, these studies are limited in the data available for adjustment/matching and likely have residual confounding. One study also found differing results (favoring anti-IL-5 agents) for severe exacerbations compared with overall exacerbations [71]. Tezepelumab has not been in widespread use for long enough to be included in these indirect comparison studies. The choice between biologic agents is also impacted by discussions with patients regarding side effect profiles and timing of injections (table 11).

Based on limited data available and our clinical experience, we take the following approach (algorithm 1 and algorithm 2):

- **Verification of persistently uncontrolled asthma** – Biologic agents are indicated only for patients whose disease is unable to be controlled with adherence to maximized inhaled controller therapies. In one database analysis from the United States, less than half of patients escalated to biologics met criteria for uncontrolled asthma, and over half had evidence of suboptimal maintenance medication adherence [80]. Additionally, nearly half of patients were only using the equivalent of step 2 or step 3 GINA therapy (table 4). The risks and costs of biologic therapies do not support their use in these patients, who are highly likely to benefit from increased adherence to or intensification of inhaled therapies. (See 'General treatment principles' above and 'Adjusting controller therapy' above.)
- **Focused assessment for other Type 2 inflammatory comorbid diseases** – Several comorbid Type 2 inflammatory conditions are common in patients with asthma and may be cotreated with specific biologic agents. Biologic agents have also been found to be particularly effective for the treatment of asthma in those

with certain type 2 comorbidities (chronic rhinosinusitis and/or nasal polyposis) [81]. Assuring optimal treatment of both diseases may significantly impact biologic agent selection. Specific examples are provided below:

- **Eosinophilic granulomatosis with polyangiitis (EGPA)** – For patients with nonsevere EGPA, mepolizumab is a preferred therapy in conjunction with systemic glucocorticoids; it is also the only asthma biologic therapy approved for EGPA treatment. The dosing of mepolizumab for this indication is higher than for asthma alone (300 rather than 100 mg every four weeks), but it is generally well tolerated. Other anti-IL-5/5R agents are also being investigated as possible therapeutic options. (See "Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Treatment and prognosis", section on 'Nonsevere EGPA' and "Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Treatment and prognosis".)
- **Allergic bronchopulmonary aspergillosis (ABPA)** – Asthma biologics are indicated in patients with ABPA who have recurrent exacerbations or inability to taper off oral glucocorticoids. Anti-IL-5/5R, anti-IL-4, and anti-IgE agent use have all been described in small case series. Our authors prefer to use mepolizumab or benralizumab in those who have a blood eosinophil count ≥300cells/microL and omalizumab in those with lower eosinophil levels. Further study is needed to determine the appropriate role for these biologics in ABPA and whether any of these agents interrupt progression of bronchiectasis. (See "Treatment of allergic bronchopulmonary aspergillosis", section on 'Use of biologic agents in ABPA'.)
- **Atopic dermatitis (AD)** – Because the anti-IL4Ra antibody dupilumab is a first-line systemic therapy for atopic dermatitis, we strongly prefer the use of dupilumab in any patients with severe asthma who require systemic AD treatment. Other asthma biologics are not useful in the management of AD. (See "Treatment of atopic dermatitis (eczema)", section on 'Biologic agents' and "Evaluation and management of severe refractory atopic dermatitis (eczema) in adults", section on 'First-line therapies'.)

- **Chronic rhinosinusitis with nasal polyposis (CRS with NP)** – CRS with NP is a frequent asthma comorbidity that can also be treated with biologic agents if control cannot be maintained following a course of systemic corticosteroids or sinus surgery and topical corticosteroid maintenance. When using biologic agents to treat patients with asthma and comorbid refractory CRS with NP, we typically choose dupilumab due to evidence of increased efficacy against nasal polyposis. Omalizumab and mepolizumab are reasonable alternatives that have also been approved for refractory CRS with NP. Benralizumab does not improve long-term symptom scores, time to surgery, or chronic corticosteroid use in treatment of nasal polyposis [82]. Although biologic agents have not been compared directly, systematic reviews of randomized trials in patients with CRS and NP suggest that dupilumab treatment leads to the largest improvements in both patient-reported and objective measures of disease. (See "Chronic rhinosinusitis with nasal polyposis: Management and prognosis", section on 'Biologic therapies'.)

- **Patients with childhood-onset asthma** – For patients with persistently uncontrolled childhood onset asthma, several studies suggest that anti-IL-5/5R therapies are much less effective as a class, even in patients with elevated eosinophils [83-88]. Dupilumab demonstrates efficacy in this subgroup, although its effects are more robust in those with later-onset [89]. In a post hoc analysis of tezepelumab trials, tezepelumab also demonstrated an approximately 50 percent reduction in exacerbations in participants with childhood-onset asthma [90]. Therefore, dupilumab, tezepelumab, and omalizumab are all reasonable options for these patients, with the optimal choice between them uncertain due to a lack of head-to-head comparisons.

  Based on post hoc analyses, omalizumab, dupilumab, and tezepelumab have shown increased impact in patients with elevated eosinophils (≥260, ≥150, and ≥300 cells/microL, respectively) or elevated fractional excretion of nitric oxide (≥19.5 ppb, or ≥25 ppb, respectively) [72,73,91,92]. In one trial, tezepelumab also showed increased efficacy in patients with higher type 2 markers (FeNO ≥25 ppb or eosinophils >450 cells/microL), but there was no differential effect based on antigen sensitivity [74]. We typically use dupilumab in patients with elevations in

both markers due to its striking efficacy (approximately 70 percent reduction in exacerbation risk) in this group in the pivotal trials [73]. For patients without elevations in either marker (non-type 2 asthmatics), tezepelumab may be particularly helpful [92], even if they otherwise qualify for omalizumab. Omalizumab is also a reasonable alternative for those with established allergen-driven symptoms.

- **Patients with adult-onset asthma without peripheral eosinophilia** – For patients without eosinophilia who have an elevated FeNO or significant allergy-driven symptoms to suggest type 2 inflammation, we often use omalizumab. Tezepelumab also shows efficacy in this group [74]. Although off-label (in the United States), there is evidence that dupilumab may be effective in those with elevated FeNO but without eosinophilia [93].

  For those without eosinophils due to chronic use of oral glucocorticoids, we typically reassess after temporary tapering or discontinuation of corticosteroids, as described above. Both anti-IL4R and anti-IL-5/5R agents have shown efficacy in dose-reducing or eliminating oral glucocorticoids in those with type 2 inflammation and systemic glucocorticoid-dependent disease (algorithm 2). (See 'Anti-IL-5 therapy' below and 'Anti-lL-4 receptor alpha subunit antibody (dupilumab)' below.)

  Among the biologic agents, tezepelumab is the only agent shown to reduce exacerbation rates in patients without either peripheral eosinophilia or allergen-driven symptoms. We use this agent preferentially in patients without signs of type 2 inflammation or for those without peripheral eosinophilia who do not qualify for omalizumab. Tezepelumab also has demonstrated efficacy in those with peripheral eosinophilia and allergen-driven disease [74,90] and is an effective agent in these settings (algorithm 1). Comparative efficacy data would be very helpful to allow more definitive guidance for optimal use of this agent. (See 'Anti-thymic stromal lymphopoietin (tezepelumab)' below.)

- **Patients with modest elevations in peripheral eosinophils (150 to 300 cells/microL)** – Dupilumab is highly effective in patients with elevated eosinophils between 150/microL and 300/microL, particularly those with an elevated FeNO

[73]. In these patients with lower elevations in eosinophils, post hoc analyses demonstrate a 40 percent reduction in exacerbation risk with dupilumab treatment [67,73,94]. Patients who also have a FeNO ≥25 ppb are even more likely to benefit. Tezepelumab has also demonstrated an approximately 40 percent reduction in exacerbation risk in this patient population in one clinical trial [74]. In contrast, the positive data for IL-5/IL-5R agents are more convincing in patients with higher peripheral eosinophils (≥300 eosinophils/microL); reslizumab requires even higher levels (>400/microL). We therefore typically use dupilumab or tezepelumab as first-line agents in this group, with IL-5/IL-5R agents reserved for patients with adult-onset asthma and multiple treatment failures. For patients with evidence of allergen sensitization, omalizumab may also be used. (See 'Anti-IL-4 receptor alpha subunit antibody (dupilumab)' below and 'Anti-IL-5 therapy' below.)

- **Patients with adult-onset asthma and large elevation in peripheral eosinophils (300 to 1500 eosinophils/microL) or eosinophil-driven comorbidities** – Because anti-IL-4R, anti-TSLP, anti-IL-5, and anti-IL-5R therapies are all effective for patients with adult-onset asthma whose disease is driven by type 2 eosinophilic inflammation, there are an abundance of reasonable choices for patients in this group.

  Dupilumab and tezepelumab have been shown to be highly effective (more than 50 percent relative risk reduction in exacerbations) in those with elevated eosinophils accompanied by an elevated FeNO (≥25 ppb) or significant allergic component of their asthma [73,74,95,96]. We typically use dupilumab or tezepelumab as first-line therapy for these patients.

  For the remainder of patients with elevated eosinophils, we often use benralizumab given its eight-week dosing cycle, but there are minimal data to distinguish between the anti-IL-5/5R biologics in this group (table 11). Mepolizumab is preferred in those with some degree of nasal polyposis, as benralizumab is not effective in treating the nasal polyps and reslizumab has not been well studied in nasal polyposis. Due to its IV formulation, we typically reserve reslizumab for patients with class III or higher obesity (table 12) who

may benefit from weight-based dosing or for those with persistent eosinophilia after treatment with other anti-IL-5/5R agents.

A post hoc analysis has also suggested that omalizumab is effective at reducing exacerbation rates in patients with peripheral eosinophils who otherwise qualify for omalizumab based on elevated IgE levels [91]. This agent is therefore also a reasonable option for this patient population.

- **Patients with hypereosinophilia (>1500 cells/microL)** – Patients with this degree of severe peripheral eosinophilia should also be evaluated for specific causes of hypereosinophilia that may require alternative treatment strategies. In patients with such severe elevations in peripheral eosinophils, dupilumab should not generally be used as it may unmask and worsen eosinophilic vasculitis (EGPA). Due to their robust anti-eosinophilic properties, anti-IL-5/5R agents are the mainstay of asthma therapy for this group when no alternative cause is identified. (See "Hypereosinophilic syndromes: Clinical manifestations, pathophysiology, and diagnosis", section on 'Evaluation and diagnosis' and 'Anti-IL-4 receptor alpha subunit antibody (dupilumab)' below.)

Anti-IgE therapy (omalizumab) — The anti-IgE agent omalizumab is approved by the United States Food and Drug Administration (FDA) for use in patients age six years and above with moderate to severe persistent allergic asthma, an IgE level of 30 to 700 international units/mL, positive allergen-skin or allergen-specific IgE tests to a perennial allergen, and incomplete symptom control with inhaled glucocorticoid treatment (table 11) [97-100].

- **Administration** – Omalizumab is administered by subcutaneous injection every two to four weeks in a dose that is determined by body weight and the levels of serum IgE (0.016 mg/kg per international units/mL of IgE per month). A dose of 150 to 375 mg is injected subcutaneously every two to four weeks to achieve the monthly target. No more than 150 mg is administered at a single injection site, to prevent local reactions. (See "Anti-IgE therapy", section on 'Administration'.)

  We typically use a three- to six-month trial before concluding benefit or lack thereof; some experts advise an initial trial of at least four months [25]. In a randomized trial (1070 participants), a composite end-point for omalizumab

response (no exacerbations and one of the following: reduced symptom score, reduced usage of rescue medication, improved lung function, improved quality of life) was met at 16 weeks by 64 percent; among these, 87 percent had responded by 12 weeks [97]. (See "Anti-IgE therapy", section on 'Administration'.)

Omalizumab is available for self-administration in the United States and other countries, using pre-filled syringes, although supervised administration is preferred [101]. Recommended selection criteria for self-administration include no prior history of anaphylaxis, successful administration of three separate doses of omalizumab in the office, ability to recognize and treat symptoms of anaphylaxis, and ability to utilize proper injection technique for subcutaneous injections of omalizumab and follow the prescribed dosing regimen [102]. (See "Anti-IgE therapy", section on 'Home administration' and "Overview of infections associated with immunomodulatory (biologic) agents".)

- **Efficacy** – Overall response rates to omalizumab (eg, reduced inhaled fluticasone dose, rescue medication use, asthma symptoms) in patients with moderate to severe asthma are variable and range from 30 to 60 percent [103]. While total IgE levels are not predictive of response, modest elevations in blood eosinophils and FeNO may identify patients who are more likely to experience a decrease in exacerbations with omalizumab [72]. Treatment with omalizumab is associated with reduced hospitalizations and oral corticosteroid use over long-term follow-up [104]. However, in one observational cohort, patients receiving omalizumab were less likely than those receiving anti-IL-5 therapies to have a robust response that included normalization of lung function and cessation of systemic glucocorticoid use [105].

  Omalizumab was assessed in 850 patients with severe asthma (poor symptom control on fluticasone 1000 mcg/d and a long-acting beta-agonist [LABA] with or without other controller medications) who were randomly assigned to omalizumab or placebo for 48 weeks [106]. A 25 percent reduction in the rate of asthma exacerbations was noted in the omalizumab group compared with placebo, although the results are somewhat limited by the 20 percent early discontinuation rate. No reduction in exacerbations was noted in the subgroup

taking daily oral glucocorticoids. However, the lack of effect in this subgroup may be due to an insufficient sample size.

The efficacy of omalizumab and patient selection are discussed in greater detail separately. (See "Anti-IgE therapy", section on 'Efficacy' and "Anti-IgE therapy", section on 'Indications and patient selection'.)

Anti-IL-5 therapy — Interleukin (IL)-5 is a pro-eosinophilic cytokine that is a potent mediator of eosinophil hematopoiesis and contributes to eosinophilic inflammation in the airways. Mepolizumab and reslizumab are anti-IL-5 monoclonal antibodies [107]; benralizumab is an anti-IL-5 receptor alpha antibody (table 11). As with other biologics agents, the response to treatment is quite heterogeneous; patients with the most robust responses to anti-IL-5 therapy are more likely to have adult-onset disease, shorter symptom duration, or a high fraction of exhaled nitric oxide (FeNO) [105].

Mepolizumab — Mepolizumab, a monoclonal antibody to IL-5, reduces exacerbations in patients with severe asthma who have blood eosinophil counts of 150/microL or greater (table 11) [108-113]. In contrast, earlier studies of anti-IL-5 antibodies, performed in patients with milder asthma that was not necessarily eosinophilic, did not show benefit [114-116].

Based on these data, Mepolizumab is used for add-on, maintenance treatment of severe asthma in patients who are age six years or older and have an eosinophilic phenotype, although some European regulators (and United States providers) recommend an absolute blood eosinophil count ≥300/microL [117-119]. Clinical trial data suggest that efficacy requires an absolute blood eosinophil count ≥150/microL [117,120], but this threshold is less clear in patients on daily systemic glucocorticoids. Mepolizumab is also approved for treatment of chronic rhinosinusitis and nasal polyposis. (See "Aspirin-exacerbated respiratory disease", section on 'Mepolizumab'.)

- **Administration and monitoring** – In adolescents and adults, mepolizumab is administered subcutaneously into the upper arm, thigh, or abdomen, 100 mg every four weeks [121]. Pre-filled safety syringes and auto-injector preparations are available for home administration in selected patients age 12 years and older, after training on technique [122,123]. Appropriate preparations should be in

place for monitoring and treatment of adverse reactions to biologic agents. Hypersensitivity reactions have been reported with mepolizumab. In addition, *Herpes zoster* infections have occurred in a small number of patients receiving mepolizumab. Based on limited data, we administer the varicella-zoster vaccine to adults age 50 years or older, four weeks prior to initiation of mepolizumab. Immunocompromised patients at risk for disseminated varicella-zoster infection (eg, due to use of prednisone ≥20 mg/day for ≥14 days) require a different vaccination strategy. (See "Vaccination for the prevention of shingles (herpes zoster)" and "Overview of infections associated with immunomodulatory (biologic) agents".)

The optimal method for determining which patients receiving mepolizumab are likely to derive long-term benefit from maintenance mepolizumab is unclear. In a post hoc analysis of two large trials, measures such as physician-assessed response, asthma symptom control, and improvement in forced expiratory volume in one second (FEV_1) at 16 weeks did not predict which patients would experience exacerbations in the following 16 or 36 weeks, respectively [109,112,124]. A decrease in peripheral blood eosinophils predicted reduced exacerbations in only one of the trials.

We typically assess response in terms of symptoms, steroid-sparing effect, and exacerbation frequency at three and six months to determine whether to continue therapy.

- **Impact on exacerbation rates and quality of life** – Several trials have found that mepolizumab improved outcomes among patients with severe asthma and blood or sputum eosinophilia [108-112,125-127]. A systematic review found high quality evidence from three randomized trials (1071 participants) that mepolizumab reduces exacerbations in patients with eosinophilic asthma (incidence rate ratio 0.49; 95% CI 0.38-0.66; approximately 592 fewer exacerbations per 1000 patients per year) [128]. Mepolizumab improved asthma control and quality of life but did not meet the minimum clinically important difference thresholds. A separate systematic review of four studies also found that mepolizumab reduced exacerbation rates by approximately one-half [107].

However, a trial of mepolizumab in children and adolescents from low-income, primarily urban, environments with eosinophilic asthma (>150 eosinophils / microL, ≥2 exacerbations per year) showed an attenuated benefit from mepolizumab compared with studies in the adult population (0.96 exacerbations per year with mepolizumab versus 1.3 per year with placebo, [RR 0.73, 95% CI 0.56 to 0.96]) [85]. Whether this lesser performance is due to ongoing environmental exposures, high non-T2 inflammation, biologic changes between childhood and adult asthma, or other differences in the overall study populations is not well understood.

- **Glucocorticoid-sparing effect** – In the SteroId ReductIon with mepolizUmab Study (SIRIUS), 135 patients with severe asthma and peripheral blood eosinophilia (300 eosinophils/microL during the 12 months prior to study entry or 150 eosinophils/microL during the optimization phase) despite maintenance systemic glucocorticoid treatment (5 to 35 mg of prednisone or its equivalent per day) were randomly assigned to mepolizumab 100 mg or placebo administered subcutaneously every 4 weeks for 20 weeks [108]. The likelihood of a reduction in the glucocorticoid dose was 2.39 times greater in the mepolizumab group (95% CI 1.25-4.56) and the mean reduction from baseline was 50 percent compared with no reduction in the placebo group. In addition, mepolizumab was associated with a decrease in the number of asthma exacerbations and improved control of asthma symptoms.

Reslizumab — Reslizumab, a monoclonal anti-IL-5 antibody, has been approved by the FDA for add-on, maintenance therapy of severe asthma in patients who are age 18 years or older and have an eosinophilic phenotype (table 11) [129,130]. In pivotal trials, an eosinophil phenotype was defined as a peripheral blood absolute eosinophil count of 400/microL or greater, although the threshold required for patients on systemic glucocorticoids is not clear. In these studies, reslizumab reduced asthma exacerbations by approximately 50 percent [107,125,131].

- **Administration and monitoring** – Reslizumab is administered 3 mg/kg by intravenous infusion over 20 to 50 minutes in a setting prepared to handle anaphylaxis [132]. Based on a frequency of anaphylaxis of 0.3 percent, the FDA has placed a boxed warning recommending a period of observation after dosing.

The most common adverse reaction was oropharyngeal pain (incidence ≥2 percent).

We assess the response to treatment (eg, exacerbations, symptom control, lung function, adverse effects) after four to six months.

- **Impact on exacerbation rates and quality of life** – Multiple studies demonstrate evidence in favor of intravenous reslizumab over placebo for eosinophilic asthma treatment [125,128,131,133-135]. A systematic review found high-quality evidence from three randomized trials (1059 participants) that reslizumab reduced exacerbations in patients with eosinophilic asthma (incidence rate ratio 0.46, 95% CI 0.37-0.58; approximately 972 fewer exacerbations per 1000 patients/year) compared with standard of care [128].

  - In two parallel group, multicenter trials, 953 patients aged 12 to 75 years whose asthma was poorly-controlled despite medium-to-high doses of inhaled glucocorticoid, blood eosinophils ≥400 cells per microL or higher, and one or more exacerbations in the previous year were randomly assigned to reslizumab 3 mg/kg or placebo intravenously every four weeks for one year [131]. The reslizumab groups experienced a significant reduction in the frequency of exacerbations (study 1: rate ratio [RR] 0.50, 95% CI 0.37-0.67; study 2: RR 0.41, 95% CI 0.28-0.59). Two patients in the reslizumab group experienced anaphylaxis, otherwise adverse events were similar between the groups.

    FEV_1 improved modestly with reslizumab compared with placebo by week 4, and the improvement persisted through week 52 (0.22 L versus 0.12 L). Reslizumab also resulted in a statistically but not clinically significant improvement in asthma quality of life and in asthma symptoms, based on the Asthma Symptom Utility Index and the Asthma Control Questionnaire-7.

  - A multicenter randomized trial assigned 315 adolescents and adults with uncontrolled asthma, despite at least medium-dose inhaled glucocorticoids, and peripheral blood eosinophilia (≥400 cells/microL) to reslizumab 0.3 mg/kg, 3 mg/kg, or placebo intravenously every 4 weeks for 16 weeks [133]. Reslizumab improved FEV_1 relative to placebo with a larger increase at the

higher dose (115 mL [95% CI, 16-215] and 160 mL [95% CI, 60-259]). Asthma symptoms and quality of life improved similarly to the above trials in the higher dose group.

- **Glucocorticoid-sparing effect** – Data on glucocorticoid sparing effects of reslizumab are limited. Post hoc analyses of pooled data from two placebo-controlled phase III trials found 73 patients in each arm who were taking oral glucocorticoids at baseline [135]. Patients receiving reslizumab were issued fewer new systemic glucocorticoid prescriptions (mean 0.5 versus 1.0 prescriptions) and received a lower total average dose over the course of the 52-week trial (250 versus 610 mg).

Benralizumab — Benralizumab is a monoclonal antibody directed against IL-5 receptor alpha that is approved by the FDA as add-on therapy in patients (≥6 years) with severe asthma and an eosinophilic phenotype (eg, peripheral blood eosinophil count ≥150 cells/microL) (table 11) [136,137]. In Canada, it is approved for age ≥18 years [138]. Benralizumab depletes IL-5 receptor-bearing cells (eosinophils and basophils) via enhanced antibody-dependent cytolysis and also blocks IL-5 binding to its receptor [139-142]. Benralizumab has repeatedly been shown to be more effective than anti-IL-5 antibody therapy in reducing eosinophil numbers, but there are less data on whether this translates to greater clinical efficacy. In one small trial of patients with residual asthma symptoms and sputum eosinophilia despite anti-IL-5 antibody therapy, benralizumab treatment over nine months was effective in eliminating sputum and blood eosinophils in all patients and improving asthma symptoms in 80 percent of those treated [143]. In one cohort, the annualized exacerbation rate was reduced by 69 percent (0.86 versus 2.8 exacerbations/year) compared with baseline among patients who had switched to benralizumab after using mepolizumab during the baseline period [144]. (See "Pathogenesis of asthma", section on 'Airway inflammation'.)

- **Administration and monitoring** – In adolescents and adults, benralizumab is given subcutaneously, 30 mg every four weeks for the first three doses, and then 30 mg every eight weeks [136]. It is supplied in a prefilled syringe and should be brought to room temperature prior to use. A pre-filled auto-injector device is approved by the FDA and European Medicines Agency (EMA) for home

administration after training on technique and with appropriate preparations for monitoring and treatment of adverse reactions to biologic agents. Pre-existing helminth infections should be treated prior to initiating benralizumab.

We assess the response to treatment (eg, exacerbations, symptom control, lung function, adverse effects) after four to six months.

In clinical trials, benralizumab was well tolerated, and the most common adverse events were headache and pharyngitis [141,142]. Hypersensitivity reactions (anaphylaxis, angioedema, urticaria) occurred in approximately 3 percent of subjects, usually within a few hours, but occasionally after a few days. Hypersensitivity is a contraindication to further use. There may be an increase in risk of parasitic infections or helminthiasis in endemic areas [145].

- **Impact on exacerbation rates and quality of life** – Three multicenter trials have demonstrated a reduction in exacerbation rates when benralizumab was given to patients with moderate or severe asthma [86,141,142].
  - In one trial (SIROCCO), 1205 adolescent and adult patients with severe asthma and at least two exacerbations in the prior year while taking high-dose inhaled glucocorticoids and a long-acting beta-agonist were randomly assigned to benralizumab 30 mg every four weeks, benralizumab 30 mg every eight weeks (after 30 mg every four weeks for three doses), or placebo every four weeks, given subcutaneously for 48 weeks [141]. Among those with a peripheral blood eosinophil count ≥300 cells/microL, benralizumab reduced the exacerbation rate in the every-four- and every-eight-week groups (rate ratio [RR] 0.55, 95% CI 0.42-0.71, and RR 0.49, 95% CI 0.37-0.64, respectively). In these patients, both benralizumab regimens improved prebronchodilator FEV_1 more than placebo (by 110 mL and 160 mL for lower and higher dose groups, respectively), and the eight-week regimen reduced asthma symptom scores by a statistically but not clinically significant degree. Among patients with peripheral blood eosinophil counts <300 cells/microL, the effect on exacerbations was of borderline significance.
  - In another trial (CALIMA), a similar population of 1306 adolescent and adult patients with poorly controlled moderate to severe asthma received

benralizumab 30 mg every four weeks, benralizumab 30 mg every eight weeks (after 30 mg every four weeks for three doses), or placebo every four weeks, given subcutaneously for 60 weeks [142]. Compared with placebo, the annual exacerbation rate among those with a peripheral eosinophil count ≥300 cells/microL decreased in the "every-four-week" benralizumab group (RR 0.64, 95% CI 0.49-0.85) and in the "every-eight-week" group (RR 0.72 [95% CI 0.54-0.95). For the smaller group of patients with lower eosinophil counts, the relative reduction in exacerbation rates was of similar magnitude but were not statistically significant. Improvements in lung function were smaller in patients with lower eosinophil counts. Benralizumab-treated patients had small but not clinically meaningful increases in quality-of-life scores.

- The multicenter ANDHI trial randomly assigned 656 adults with severe eosinophilic asthma (peripheral eosinophil count ≥150 cells/microL and ≥2 exacerbations in the prior year) to benralizumab or placebo for 24 weeks [86]. Benralizumab decreased annual asthma exacerbations compared with placebo (RR 0.51, 95% CI 0.39-0.65).

Similar results have been seen in other trials and observational studies [144,146,147].

- **Glucocorticoid-sparing effect** – A glucocorticoid-sparing effect with benralizumab has been found in two multicenter studies [146,147].
  - In one trial (ZONDA), after a run-in phase that determined the minimum oral glucocorticoid dose needed to maintain asthma control, 220 patients with severe asthma who had ≥150 eosinophils/microL in peripheral blood **and** required daily oral glucocorticoids for the previous six months were randomly assigned to one of three treatment arms: benralizumab 30 mg subcutaneously every four weeks, benralizumab 30 mg every four weeks for the first three doses then every eight weeks, or placebo every four weeks [146]. Oral glucocorticoids were tapered after the first four weeks according to a predetermined program (2.5 to 5 mg every four weeks depending on symptoms). After 28 weeks, the oral glucocorticoid dose decreased by 75 percent from baseline in the two benralizumab groups, compared with 25

percent in the placebo group. Annualized exacerbation rates were significantly lower in the benralizumab group despite the decreased steroid dosing.

- An open-label study (POTENTE) evaluated the safety of protocolized glucocorticoid withdrawal in 598 patients with oral glucocorticoid-dependent asthma treated with benralizumab every four weeks for three doses and every eight weeks thereafter [147]. Oral glucocorticoids were successfully eliminated in 62 percent of patients, and another 20 percent were tapered to 5 mg or less, with continued use solely for adrenal insufficiency. Exacerbations requiring urgent medical care occurred in 6 percent; the overall exacerbation rate was 0.63 per patient annually.

These data suggest that protocolized weaning of steroids is safe and effective for patients using benralizumab.

Anti-IL-4 receptor alpha subunit antibody (dupilumab) — Dupilumab is a fully human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor. Through blockade of this receptor, dupilumab inhibits the activity of both IL-4 and IL-13, Type 2 cytokines that play a key role in allergy and asthma. Dupilumab reduces asthma exacerbations, enables oral glucocorticoid tapering, and improves lung function [73,148-151]. Dupilumab is approved by the FDA for the treatment of moderate-to-severe, eosinophilic asthma (eg, peripheral blood eosinophils ≥150/microL) in patients age six years and older [152]. (See "Pathogenesis of asthma", section on 'Th2 lymphocytes' and "Evaluation and management of severe refractory atopic dermatitis (eczema) in adults", section on 'Dupilumab'.)

- **Administration and monitoring** – The recommended dose of dupilumab for adolescents and adults is an initial 400 mg (two 200 mg subcutaneous injections), followed by 200 mg given every other week **or** an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week. The higher dose is suggested for patients with oral glucocorticoid-dependent asthma or comorbid moderate to severe atopic dermatitis. Patients may self-administer injections at home after proper training and with appropriate preparations for monitoring and treatment of adverse reactions to biologic agents.

Pre-existing helminth infections, such as echinococcus or strongyloidiasis, should be treated prior to initiation of dupilumab. (See "Infectious causes of peripheral eosinophilia" and "Echinococcosis: Treatment" and "Strongyloidiasis".)

We assess the response to treatment (eg, exacerbations, symptom control, lung function, adverse effects) after four to six months.

Adverse effects of dupilumab include injection site reactions (in about 15 percent) and transient eosinophilia (4 to 14 percent) with over 3000 cells/microL in many of these patients (1 to 13 percent) [73,150,153]. Most of the eosinophilia occurred in those with high baseline eosinophil levels (>500 cells/microL) and was not associated with symptoms or discontinuation of therapy [153]. New systemic symptoms (eg, arthralgias, fevers, rash) while on dupilumab should prompt reassessment of peripheral eosinophil levels, as eosinophilia (>1500 cells/microL) can occur months to years after starting treatment. Development or worsening of hypereosinophilic syndrome and eosinophilic granulomatous polyangiitis have been reported [149,154].

Antidrug antibody responses were noted in 2 to 5 percent of dupilumab-treated patients and in 1 to 5 percent of placebo-treated groups but did not appear to affect efficacy [73,150].

One study analyzing nearly 38,000 case reports of rare adverse reactions to dupilumab found a significant increase in risk for development or worsening of several Th17-driven diseases [155]. Seronegative arthritis, psoriasis, enthesitis/enthesopathy, and iridocyclitis were positively associated with dupilumab use, but ankylosing spondylitis was not. The plausible theorized mechanism based on animal studies is that the IL-4/IL-13 axis may act as a restraint on Th17 (as well as Th1) responses. Inhibition of IL-4/IL-13 by dupilumab therefore may bias the immune response towards Th17-associated autoimmune conditions in patients with a predisposition to these diseases. Whether similar effects on Th1 inflammation occur remains to be understood.

- **Impact on exacerbation rates and quality of life** – In a multicenter trial, 1902 patients ages 12 years or older with poorly controlled asthma were randomly assigned to one of two add-on dupilumab doses (200 mg after a loading dose of

400 mg **or** 300 mg after a loading dose of 600 mg) or placebo, administered subcutaneously every two weeks for 52 weeks [73]. The annualized rates of severe exacerbations were decreased by approximately one-half in the dupilumab groups (eg, 0.46 per year [95% CI 0.39-0.53] in the 200 mg of dupilumab group compared with 0.87 [95% CI 0.72-1.05] in the placebo group). There were moderate and statistically significant increases in FEV_1 (approximately 0.15 L) with both doses of dupilumab compared with placebo. In a prespecified analysis, the treatment effect was dependent on baseline blood eosinophil count, with a relative reduction in exacerbation rate of 67 percent, 40 percent, and minus 4 percent among participants with a baseline blood eosinophil count of ≥300/microL, 150 to 299/microL, and <150/microL, respectively. However, in a post hoc analysis, dupilumab improved asthma exacerbation rates by 69, 58, and 22 percent compared with placebo in patients with an FeNO ≥50, 25 to 50, or <25, respectively, an effect that was found to be independent of blood eosinophil level [93].

In additional post hoc analyses, dupilumab improved exacerbations equally well in patients with ≥150 eosinophils/microL regardless of whether they had an allergic asthma phenotype (elevated total and one specific IgE) [156] but had a less robust effect on exacerbation reduction in those with disease onset before age 18 years compared with those having later-onset disease [89]. Compared with placebo, there were minimal effects of dupilumab treatment on patient reported outcomes (eg, asthma control and asthma quality of life) in the initial trial, although a post hoc analysis reported a clinically meaningful improvement in asthma control in patients with a blood eosinophil count >500/microL [157]. Safety and efficacy were durable for an additional two years beyond the initial study [158], and even patients with exacerbations on dupilumab during the randomized trial had substantial declines in subsequent exacerbations during longer-term treatment [159].

- **Glucocorticoid-sparing effect** – In a separate trial, 210 participants 12 years of age or older with oral glucocorticoid-dependent asthma were randomly assigned to dupilumab 300 mg (after a loading dose of 600 mg) or placebo, subcutaneously, every two weeks for 24 weeks [150]. At the start of the study, the

mean oral glucocorticoid dose was 11 mg/day of prednisone (or equivalent, range 5 to 35 mg/day). The dose was tapered from week 4 to week 20, as tolerated, according to a predefined protocol. The oral glucocorticoid dose decreased by 70 percent in the dupilumab group and by 42 percent in the placebo group; 80 percent of dupilumab-treated patients versus 50 percent of placebo-treated patients had a dose reduction of at least 50 percent. Despite the decrease in oral glucocorticoid dose, the exacerbation rate was lower with dupilumab than with placebo (RR 0.59, 95% CI 0.37-0.74). In a 96-week open-label extension, all participants received dupilumab for asthma control [160]. There was a sustained reduction in oral glucocorticoid use for those who continued dupilumab, as well as a reduction in those who switched to dupilumab from placebo. The relatively slow oral glucocorticoid wean in the extension study compared with the rapid down-titration in the initial study argues in favor of a more aggressive and protocolized weaning strategy after dupilumab initiation.

Anti-thymic stromal lymphopoietin (tezepelumab) — Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that participates in asthma inflammation. Tezepelumab is a human monoclonal immunoglobulin G2-lambda antibody (AMG 157) that binds TSLP and prevents its interaction with the TSLP receptor complex [161]. Tezepelumab is approved by the FDA for add-on maintenance therapy in patients with severe asthma who are ≥12 years of age [162].

- **Administration and monitoring** – The standard dose of tezepelumab is 210 mg, administered subcutaneously every four weeks. A minimum baseline level of blood eosinophils or FeNO is not required. Hypersensitivity and anaphylactic reactions have been reported, including reports of delayed onset reactions. A prefilled auto-injector device is approved by the FDA for home administration after training on technique and with appropriate preparations for monitoring and treatment of adverse reactions to biologic agents [162].
- **Impact on exacerbation rates and quality of life** – Two pivotal trials demonstrated a reduction in asthma exacerbations among patients with severe asthma treated with tezepelumab:

- In one trial (PATHWAY), 550 patients with moderate to severe asthma with at least two asthma exacerbations or one exacerbation that required hospitalization in the previous year despite appropriate inhaled therapies (LABA-ICS) were assigned to placebo or one of three different doses of tezepelumab (70 mg every four weeks, 210 mg every four weeks, or 280 mg every two weeks) [96]. After 52 weeks, the tezepelumab groups all had similar decreases in exacerbation rates compared with placebo (relative decreases of 61 percent, 71 percent, and 66 percent, respectively). Additional analyses showed small improvements in standardized asthma symptom and quality-of-life scores and a significantly lower proportion of patients requiring emergency care (1.2 percent versus 3.6 percent) [163,164].

- In a subsequent trial (NAVIGATOR) that included 1059 participants (age 12 to 80 years) with severe uncontrolled asthma (618 with eosinophil count ≥300 cells/microL; 441 with eosinophil count <300 cells/microL), 210 mg of tezepelumab or placebo were administered every four weeks for 52 weeks on a background of continued inhaled controller therapy [74]. On average, tezepelumab reduced exacerbations by 1.2 per year, a 56 percent relative reduction (0.93 versus 2.1 per year with placebo, rate ratio [RR] 0.44, 95% CI 0.37-0.53). In the tezepelumab group, 32 exacerbations were associated with emergency room or inpatient care compared with 149 in the control group (RR, 0.21; 95% CI 0.12-0.37). Other secondary outcomes included small, not clinically significant improvements in asthma control and quality of life by standardized questionnaires and a modest improvement in prebronchodilator FEV_1 compared to baseline (+0.14 L mean difference between tezepelumab and placebo). These benefits were durable over an additional 52 weeks with a generally favorable safety profile [165].

- A post-hoc analysis pooling data from both trials (of 210 mg tezepelumab every four weeks versus placebo) demonstrated tezepelumab-associated reductions in asthma-associated exacerbations ranging from 37 percent in patients with both FeNO <25 ppb and blood eosinophil count <150 cells/microL (0.7 versus 1.1 exacerbations per year, RR 0.63, 95% CI 0.4-1.0) to 73 percent in those with both FeNO ≥25 ppb and blood eosinophil count ≥300 cells/microL

(0.65 versus 2.9 exacerbations/year, RR 0.23, 95% CI 0.16-0.31) [166]. Severe exacerbations requiring emergency department visit or hospitalization were reduced by 60 to 90 percent across FeNO and blood eosinophil count subgroups and by 79 percent in the total studied population (0.06 per year with tezepelumab versus 0.26 per year with placebo, RR 0.21, 95% CI 0.13-0.35). Oral glucocorticoid use and allergy to perennial aeroallergen did not impact the effect on acute exacerbations. Severe adverse events were generally lower in the tezepelumab-receiving patients (9 percent versus 13 percent with placebo), but cardiac events were increased (0.8 percent versus 0.3 percent with placebo).

- **Glucocorticoid-sparing effect** – In a separate trial (SOURCE), 150 patients with poorly controlled moderate to severe asthma were optimized on oral glucocorticoid therapy for eight weeks, assigned tezepelumab 210 mg every four weeks or placebo, and then placed on a symptom-based protocolized glucocorticoid taper [167]. There was not a significant effect on oral glucocorticoid reduction in the tezepelumab group compared with placebo. However, there was evidence of improved glucocorticoid requirements in the prespecified subgroup of participants with a blood eosinophil count ≥150 eosinophils/microL.

Nonbiologic therapies — For patients with persistently uncontrolled asthma who do not qualify for or cannot obtain biologic therapies, additional options include a trial of macrolide antibiotics and bronchial thermoplasty.

Macrolide antibiotics — Macrolide antibiotics have both antimicrobial and anti-inflammatory actions raising the possibility of benefit in severe asthma, but data are conflicting [168-171]. Azithromycin may benefit selected patients based on the following studies:

- In a randomized trial (AMAZES), 420 adults with asthma that was poorly-controlled despite therapy with an inhaled glucocorticoid and a long-acting beta-agonist were assigned to add-on therapy with azithromycin 500 mg or placebo three times weekly for 48 weeks [172]. Azithromycin decreased the rate of exacerbations (incidence rate ratio [IRR] 0.59, 95% CI 0·47-0·74) and improved

asthma-related quality of life, with some suggestion that the treatment worked better in eosinophilic patients (as defined by sputum or blood eosinophilia). Diarrhea was more common in participants taking azithromycin (34 percent), compared with placebo (19 percent). Patients were excluded if they had hearing impairment or QT interval prolongation.

- In a smaller trial (AZISAST), the effect of azithromycin was examined in 109 adults with severe asthma and two exacerbations or lower respiratory tract infections requiring antibiotics in the previous year [170]. Participants were randomly assigned to azithromycin 250 mg (after an initial course of 250 mg daily for five days) or placebo three times a week for 26 weeks. No significant between group differences were noted in the rate of exacerbations or lower respiratory infections, pulmonary function, or use of rescue medication. A significant improvement was noted in the asthma quality of life questionnaire (AQLQ) score in the azithromycin group. A prespecified subgroup analysis found that azithromycin decreased exacerbations in participants with noneosinophilic asthma (blood eosinophils ≤200/microL), but not those with eosinophilic asthma.

Thus, the two largest trials of azithromycin in asthma gave conflicting results, with the largest suggesting greater efficacy in eosinophilic asthma, and the smaller suggesting no efficacy in that group.

Patients who provide a history of onset of asthma after an acute respiratory illness may respond to macrolide antibiotics on the basis of a mycoplasma or chlamydia-related initiating event [173,174]. We usually prescribe clarithromycin or azithromycin for a four- to six-week trial in patients who report onset of asthma after a respiratory illness suggestive of these organisms.

Bronchial thermoplasty — Bronchial thermoplasty (BT) refers to a technique of applying heat (via a device that delivers localized controlled radiofrequency waves) to the airways during bronchoscopy, which reduces the increased mass of airway smooth muscle associated with asthma [175-185]. Due to the risk of the procedure and modest degree of improvement, additional data are needed regarding long-term effects and morphologic changes in the airways in order to determine the ideal role for BT in asthma. Thus, for patients who meet criteria for BT (ie, poorly controlled

asthma despite high-dose inhaled glucocorticoids and a long-acting beta-agonist, nonsmoker for ≥1 year, forced expiratory volume in one second [FEV_1] ≥60 percent of predicted, no history of a life-threatening exacerbation, <3 hospitalizations in the previous 12 months, and willingness to accept the risk of an asthma exacerbation requiring hospitalization as a consequence of the procedure), we advise undergoing BT in the context of a clinical trial or registry [1,25,186]. Of note, a focused update of the National Asthma Education and Prevention Program (NAEPP) guidelines conditionally recommended against BT citing low certainty of evidence of benefit [187].

The FDA has approved marketing of Alair Bronchial Thermoplasty System for the treatment of adults (≥18 years old) with severe asthma not well-controlled with inhaled glucocorticoids and long-acting beta-agonists [188]. Bronchial thermoplasty is also approved in the European Union. However, all of the trials excluded subjects with more than three exacerbations per year or an FEV_1 <50 percent of predicted, so the safety and efficacy of BT for these patients is not known.

The procedure typically entails three separate bronchoscopies under moderate sedation about three weeks apart. A radiofrequency controller and a specialized catheter are used to administer thermal energy (target tissue temperature 65˚C) to the airway walls. All accessible airways distal to the mainstem bronchus that are 3 to 10 mm in diameter are treated once, except those in the right middle lobe, which are left untreated due to difficulty with access.

Several trials and systematic reviews and a "real-world" study have assessed the effectiveness of BT [1,178,183,184,186,189-194]; overall, BT compared with a sham procedure does not improve asthma control or hospitalizations, but may reduce severe exacerbations [183].

- One systematic review and meta-analysis included three trials (429 participants) and found improved quality of life at 12 months that did not reach clinical significance, no difference in symptoms, and no difference in pulmonary function parameters [186]. The exacerbation rates were lower with BT in two of the trials, but there was an increase in hospitalization for respiratory events during the treatment period. Overall, the benefits were felt to be modest based on moderate

quality evidence. These conclusions were similar to those from an independently performed GRADE analysis as part of the American Thoracic Society (ATS)-European Respiratory Society (ERS) guidelines on Severe Asthma [1]. Additionally, both studies suggested that performing the procedure as part of a registry such that data could be collected on safety and efficacy was also important.

- In the Asthma Intervention Research (AIR2) trial of BT for severe asthma, 288 patients with a prebronchodilator FEV_1 ≥60 percent of predicted were randomly assigned to BT or a sham procedure [189]. Patients with a history of life-threatening asthma or three or more hospitalizations for asthma in the previous year were excluded. A statistically, but not clinically significant, improvement in the primary endpoint, Asthma Quality of Life Questionnaire (AQLQ), was noted. Sixteen subjects (8 percent) in the BT group required 19 hospitalizations for acute respiratory symptoms in the six-week post-treatment period, compared with two control subjects (2 percent) who required one hospitalization each.

  In a follow-up of 162 patients who underwent BT in the AIR2 trial, the proportions of subjects experiencing exacerbations or emergency department visits in years one to five were lower by 44 and 78 percent, respectively, compared with the year before BT [190]. Prebronchodilator FEV_1 values remained stable in years one to five despite an 18 percent reduction in the average daily inhaled glucocorticoid dose. However, there was no follow up of the control group, making comparisons difficult.

- In a trial of 112 subjects with moderate or severe asthma (prebronchodilator FEV_1 60 to 85 percent of predicted) who were randomly assigned to BT or control (but without sham control), BT reduced the frequency of mild exacerbations in patients with moderate to severe persistent asthma, although there was no effect on the rate of severe exacerbations [178].

- In the Research In Severe Asthma (RISA) trial, 32 patients with severe asthma (prebronchodilator FEV_1 ≥50 percent of predicted) were randomly assigned to BT or control (without sham procedure), but investigators were not blinded [191]. BT resulted in an initial worsening of asthma control and seven hospitalizations for asthma among the 15 treated patients. However, after the perioperative period,

the BT group experienced improvements in rescue medication use and Asthma Control Questionnaire scores that persisted for the next 52 weeks of the study.

A five-year follow-up study of 14 of the original 15 who underwent BT found a decrease in hospitalizations and emergency department visits in each of the succeeding years compared with the one year prior to BT [192]. Lung function and medication use remained stable. The patient who did not consent to participation in the follow-up study died three years following BT, although the circumstances of the patient's death and whether it was caused by sequelae of asthma or BT were not available.

- In a subsequent "real-world" study (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma or PAS2) [193], 190 patients treated with bronchial thermoplasty were compared with the 190 patients treated with bronchial thermoplasty in the AIR2 trial described above [189]. The PAS2 participants, compared with AIR2 participants, experienced more exacerbations (74 versus 52 percent) and hospitalizations (15.3 versus 4.2 percent) in the prior 12 months. At three years after bronchial thermoplasty, severe exacerbations, emergency department visits, and hospitalizations decreased significantly in the PAS2 participants by 45 percent, 55 percent and 40 percent, respectively, which is comparable to the AIR2 results. However, adverse reactions, such as severe exacerbations (55.8 percent) and emergency department visits (15.8 percent), were more frequent during the treatment phase than in AIR2.

A follow-up study, which included approximately half of the participants from three randomized trials (AIR, AIR2, and RISA) [178,189,191], found similar proportions of severe exacerbations per year at 10, 5, and 1 year(s) after BT (25, 22, and 24 percent, respectively) [195]. While the participants in this study had similar baseline characteristics to those who did not have follow-up data, the loss to follow-up and differences between trials limit the conclusions that can be drawn. Quality of life measurements and spirometry were also constant over time. In terms of safety, 6 (7 percent) of 89 participants in the BT group who had not had bronchiectasis at baseline developed bronchiectasis on the 10-year high-resolution computed tomography scan (HRCT).

TAPERING THERAPY

When asthma control is achieved, the first step is to taper and discontinue oral glucocorticoids (GCs). Reducing the dose of other controller medications is based on perceived efficacy, presence of adverse effects, patient preference, and cost considerations.

Reducing the dose of inhaled GCs may be considered in patients who achieve near-complete or complete asthma control, once oral GCs have been discontinued. Guidelines for tapering of inhaled GCs have not been validated, but we usually decrease by 20 to 25 percent increments at one to three-month intervals to a medium or low dose [196]. We usually do not discontinue inhaled GCs in patients with a history of severe asthma [197]. This is otherwise essentially the same approach used for patients without severe asthma. (See "Ongoing monitoring and titration of asthma therapies in adolescents and adults", section on 'Decreasing (stepping down) therapy'.)

For patients on biologic therapies who have tapered off systemic glucocorticoids and have maintained good asthma control, it is reasonable to also step down inhaled controller therapies to achieve lower inhaled GC doses. Some patients may tolerate anti-inflammatory reliever therapy (table 13) with only biologics as maintenance agents, but the long-term safety of this approach is uncertain.

- One randomized trial has examined tapering of inhaled glucocorticoid therapy in patients well-controlled on a biologic agent. In this open-label trial (SHAMAL), 125 patients with a history of severe asthma well-controlled on benralizumab and high-dose inhaled glucocorticoids were assigned to a 32-week tapering protocol of ICS-formoterol and compared with 43 similar patients maintained on benralizumab and high-dose ICS-formoterol [198]. Tapering was based on asthma control questionnaire [ACQ] and use of as-needed ICS-formoterol; 92 percent of patients in the tapering arm successfully tapered ICS-formoterol (15 percent to medium-dose maintenance and reliever therapy [MART], 17 percent to low-dose MART, and 61 percent to as-needed ICS-formoterol). Exacerbation rates were low (≤0.15 exacerbations per year) in both groups, with only 9 percent of those in the

tapering group experiencing an exacerbation during tapering. Rates of adverse and serious adverse events, including those due to asthma, were similar in the two groups, and there were no deaths in either group. However, those using the least as-needed ICS-formoterol after the taper had significant decreases in forced expiratory volume in one second [FEV_1] and increases in fraction of exhaled nitric oxide. Thus, the safety and efficacy of tapering to as needed ICS-formoterol in these patients with more severe asthma requires further study.

The best approach to tapering patients on biologic therapies with good asthma control off their biologics has not yet been determined and is understudied. We cautiously extend dosing intervals in patients who have had excellent asthma control for more than a year on asthma biologics, typically in combination with administration of Step 4 or higher inhaled therapies (eg, medium-dose ICS-LABA). Those who tolerate one-third of the usual dosing frequency for over a year without significant exacerbation or worsening symptoms are good candidates for discontinuation. We return to the previous well-tolerated dosing schedule for patients who experience exacerbations or worsening symptoms.

- In one trial, 296 patients who had been receiving mepolizumab for three years were randomly assigned to placebo or continued mepolizumab and followed for 52 weeks [199]. Although 41 percent of patients remained exacerbation-free, there was a progressively increasing difference in the cumulative number of patients who experienced a clinically significant exacerbation over the course of the trial (59 versus 46 percent at week 52, OR 1.99, 95% CI 1.19-3.32). There was also higher unscheduled health care resource use in the discontinuation group (66 versus 49 percent, HR 1.81, 95% CI 1.31-2.49) and greater patient-perceived asthma worsening (68 versus 47 percent at 52 weeks) [200].
- In a separate small, open-label trial, 72 patients free from exacerbations and with low blood eosinophil counts on anti-IL-5/5R therapies were randomly assigned to either continue treatment or receive a taper (prolonging intervals between doses, with possible cessation of therapy if prolonged intervals were well-tolerated) [201]. Dosing intervals were returned to the previous step for exacerbations, decline in lung function, or blood eosinophil count ≥300/microL. Although 78 percent of patients were able to tolerate at least one titration step, only 22

percent of patients successfully discontinued IL-5 therapy, and exacerbations were considerably more common in the titration group than the therapy continuation group (32 versus 17 percent).

RARELY USED MEDICATIONS

- **Theophylline** – Oral theophylline has been used as an additional controller agent, although data are lacking regarding its efficacy when added to inhaled GC and a LABA. It is usually not as efficacious as LABAs when compared head-to-head [25,202-204]. Studies of withdrawal of theophylline from patients with severe asthma have demonstrated a high rate of asthma flares, suggesting that theophylline may play a role beyond its weak bronchodilator capacity [205]. (See "Theophylline use in asthma".)
- **Chromones** – Cromolyn sodium, a mast cell stabilizing medication from the chromone class (also called cromoglycates), is not effective enough to be of benefit in severe asthma and has only limited availability [8,25].

EXPERIMENTAL APPROACHES

Various pharmacologic and nonpharmacologic agents have been used in an attempt to improve asthma control and ameliorate the many adverse effects of chronic oral GC therapy in patients with severe asthma. A number of investigational therapies, such as agents targeting IL-33 and novel glucocorticoid receptor agonists, are reviewed in more detail separately. (See "Investigational agents for asthma".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Severe asthma in adolescents and adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Inhaled corticosteroid medicines (The Basics)" and "Patient education: How to use your soft mist inhaler (adults) (The Basics)" and "Patient education: How to use your dry powder inhaler (adults) (The Basics)" and "Patient education: How to use your metered dose inhaler (adults) (The Basics)" and "Patient education: Asthma in adults (The Basics)" and "Patient education: Medicines for asthma (The Basics)")
- Beyond the Basics topics (see "Patient education: Asthma treatment in adolescents and adults (Beyond the Basics)" and "Patient education: Inhaler techniques in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definition** – The American Thoracic Society (ATS) classification of "severe asthma" refers to patients who require high-dose inhaled or near continuous oral glucocorticoid (GC) treatment to maintain asthma control (table 1). (See 'Introduction' above.)
- **General treatment principles**
  - A written action plan should be provided to all patients with severe asthma; the plan may be symptom or peak flow based, or both. (See 'Patient education'

above.)

- Inhaler technique should be observed and corrected when necessary. (See 'Patient education' above.)
- Exposure to asthma triggers (eg, pets, dust mites, workplace exposures, tobacco smoke) should be controlled as much as possible (table 2). However, allergen control measures will have little to no benefit in patients without an allergic component to their disease. (See 'Controlling asthma triggers' above.)
- Treatment of comorbid diseases may be helpful. In particular, every effort should be made to achieve smoking cessation, because ongoing smoking is a risk factor for fatal asthma. (See 'Treatment of comorbidities' above.)

- **Oral glucocorticoids** – Some patients with severe asthma may need intermittent or chronic oral GC therapy in addition to high-dose inhaled GC. However, with the introduction of Type 2 biologics, the proportion of such patients is declining. For patients with chronic airflow limitation, a two-week trial of oral GCs may help determine the potential for reversibility and define a goal for future adjustments in inhaled GC. (See 'Systemic glucocorticoids' above.)
- **Additional controller medications**
  - In addition to inhaled GCs, we suggest that patients with severe asthma be started on a long-acting beta-agonist (LABA) (**Grade 2B**). However, if asthma symptoms, short-acting beta-agonist (SABA) use, and objective measures are unimproved after a trial of LABA therapy, the LABA is probably not helping and can be discontinued. (See 'Combination inhaled GC/LABA' above and "Initiating asthma therapy and monitoring in adolescents and adults", section on 'Patients with daily activity limitations (Step 4)'.)
  - In patients who do not achieve adequate control with a combination of a high-dose inhaled GC and LABA, we suggest adding or substituting an alternate controller medication (**Grade 2C**). Choices include an antileukotriene agent or tiotropium. If asthma control does not improve after a reasonable trial the added medication should be discontinued. (See 'Antileukotriene agents' above and 'Inhaled GC/LAMA or GC/LAMA/LABA' above.)

- **Biologic agents** – For patients with severe asthma not controlled with the above therapies who have an increased blood eosinophil count or elevated fractional exhaled nitric oxide (FeNO), we recommend adding a biologic agent with activity against Type 2 inflammation, such as anti-immunoglobulin (Ig)E (omalizumab), the anti-interleukin (IL)-5 agents (mepolizumab, benralizumab, reslizumab), anti-IL-4 subunit alpha (dupilumab), or anti-thymic stromal lymphopoietin (TSLP) (tezepelumab), rather than systemic glucocorticoids (**Grade 1B**). Selection among the biologic agents is guided by certain patient features (eg, age, age at asthma onset, IgE level, blood eosinophil level, comorbidities), medication administration features (frequency, availability of home administration), and medication availability (table 11 and algorithm 1). (See 'Selecting among biologic agents' above.)

  For patients with severe, uncontrolled asthma who do not have evidence of Type 2 or IgE-mediated inflammation, we suggest addition of tezepelumab rather than oral glucocorticoids or other agents (**Grade 2B**). (See 'Selecting among biologic agents' above.)

  For patients with severe, uncontrolled asthma receiving chronic oral GC therapy, dupilumab and anti-IL-5/5R biologics are the most effective glucocorticoid-sparing agents (algorithm 2). (See 'Selecting among biologic agents' above.)

  - **Omalizumab** is approved for patients ≥6 years of age with a serum IgE level of 30 to 700 international units/mL and documented sensitivity to a perennial allergen. Dosing is based on weight and IgE level. If asthma control does not improve after a reasonable trial (three to six months) the added medication should be discontinued. (See 'Anti-IgE therapy (omalizumab)' above.)
  - **Mepolizumab** is approved for ≥6 years of age; in adolescents and adults the typical dose is 100 mg, subcutaneously, every four weeks. For nonimmunocompromised adult patients age 50 years and older who are not vaccinated against *Herpes zoster*, we perform varicella-zoster vaccination four weeks prior to initiation of mepolizumab. (See 'Mepolizumab' above and "Vaccination for the prevention of shingles (herpes zoster)".)

- **Reslizumab** is approved for age 18 years and older and is administered 3 mg/kg, intravenously, every four weeks. (See 'Reslizumab' above.)
- **Benralizumab** is approved for age six years and older; adolescent and adult dosing is 30 mg subcutaneously every four weeks for the first three doses, and then 30 mg every eight weeks. (See 'Benralizumab' above.)
- **Dupilumab** is approved for age ≥6 years; in adolescents and adults it is typically administered 400 mg subcutaneously for the first dose followed by 200 mg every two weeks **or** 600 mg for the first dose followed by 300 mg every two weeks. (See 'Anti-lL-4 receptor alpha subunit antibody (dupilumab)' above.)
- **Tezepelumab** is approved for add-on maintenance therapy in patients with severe asthma who are ≥12 years of age. A minimum baseline level of blood eosinophils or FeNO is **not** required, although patients with eosinophilic asthma tend to have a slightly better response. The dose is 210 mg administered subcutaneously every four weeks. (See 'Anti-thymic stromal lymphopoietin (tezepelumab)' above.)

- **Bronchial thermoplasty** – Bronchial thermoplasty involves targeted application of heat (via radiofrequency waves) to the airways. Due to the risk of the procedure and modest degree of improvement in asthma, we rarely use BT. (See 'Bronchial thermoplasty' above.)
- **Potential alternatives** – Potential alternative and experimental therapies include macrolide antibiotics and investigational agents targeting IL-33 and novel glucocorticoid receptor agonists, as described separately. (See 'Experimental approaches' above and "Investigational agents for asthma".)

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